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ETHANOL 'DOSE-DEPENDENT' ELIMINATION: MICHAELIS-MENTEN *V* CLASSICAL KINETIC ANALYSIS

R.E. RANGNO, J.H. KREEFT & D.S. SITAR

Clinical Pharmacology Division, Montreal General Hospital Research Institute, Montreal, Quebec, Canada

1 To compare classical linear regression techniques and a Michaelis-Menten elimination model eight normal human volunteers each received three intravenous doses (0.375, 0.5, and 0.75 g/kg) of ethanol and four of the subjects each received four oral doses (0.5, 0.65, 0.95, 1.25 g/kg) of ethanol.

2 Computerized analysis of the time-plasma concentration profiles using a two-compartment Michaelis-Menton elimination model yielded a median absorption constant of 1.29 h^{-1}; volume of distribution of 0.47 l/kg; V_{max} of 0.12 g h^{-1} kg^{-1}; and K_m of 0.03 g/l. Classical techniques resulted in a slope of 0.20 g l^{-1} h^{-1}, volume of distribution of 0.55 l/kg, and a B_{60} of 0.11 g h^{-1} kg^{-1}.

3 Transient post-prandial decreases in elimination slope occurred at higher oral doses. A trend of increasing slope with increasing oral dose was seen at concentrations well above the K_m. Time to sobriety (0.8 g/l) increased nonlinearly with increasing peak concentration.

4 Maximal ethanol elimination rates are determined equally well by the two techniques. Classical analyses overestimate the volume of distribution of ethanol by 17%. Neither technique helps explain the post-prandial changes in slope or increasing slope with dose at high concentrations.

Introduction

The classical view of ethanol kinetics in humans holds that elimination proceeds at a constant rate (zero-order process) until almost all of the ethanol has been eliminated. This view has been perpetuated by many investigators with the use of arithmetic linear regression techniques and Widmark's coefficients (Kopun & Propping, 1977; Newman, Lehman & Cutting, 1937; Vesell, Page & Passananti, 1971). Haggard & Greenberg (1934) first suggested concentration-dependent elimination rates for ethanol and Lundquist & Wolthers (1958) showed that the Michaelis constant derived from experiments in man closely approximated that for alcohol dehydrogenase (ADH) *in vitro*. Wagner *et al.* (1976) and Wilkinson *et al.* (1976, 1977a) employed computer-fitting to estimate the Michaelis constants for ethanol in a one-compartment open model. Dedrick & Forrester (1973) suggested a two-compartment model with allowance for hepatic blood flow. Vestal *et al.* (1977) also used a two-compartment open model. Most of these investigators administered ethanol by the oral (p.o.) route in single, relatively small doses which achieved blood ethanol concentrations generally less than those of medicolegal interest (i.e. < 0.80 g/l). Vestal *et al.* (1977) used a small intravenous (i.v.) dose and samples for a restricted time. The aim of our investigation was to study the absorption, distribution and elimination of several larger p.o. and i.v. doses of ethanol in normal man using computerized curve fitting with a two-compartment open model with Michaelis-Menten elimination. This data was compared with that derived by classical methods.

Methods

Eight normal healthy male volunteers gave written consent to participate. Their median age was 28 years (range 24–32) and median weight 78 kg (range 56–82) kg. All subjects were in the range of ideal weight based on a standard life insurance table. All subjects had normal hepatic and renal function as measured by serum bilirubin, SGOT, LDH, BUN and creatinine. All were occasional social drinkers who consumed no ethanol for 48 h prior to a study day. They were taking no medications. Six subjects smoked less than one packet of cigarettes daily. Smoking was not a reason for exclusion of a volunteer since it has been shown that it does not affect the elimination of ethanol (Vestal *et al.*, 1977). All studies commenced at 07.00 h, the subjects having fasted for 12 h. Subjects maintained a sitting position and an indwelling catheter was placed in an antecubital vein for sampling using a heparin (10 U/ml) in saline lock between samples. A light lunch at 12.00 h and dinner at 17.00 h was provided when necessary.

Ethanol dosing was aimed at achieving peak plasma ethanol concentrations ranging from 1 to 2 g/l

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assuming a volume of distribution of 65% of body weight. The solutions of ethanol for i.v. dosing were prepared by adding absolute ethanol (Demers Lab) to normal saline for final concentrations of 5, 7, 5 and 10 g/100 ml. Doses for the i.v. route were 0.375, 0.50 and 0.75 g/kg administered by constant infusion over 30 min. Two solutions of ethanol for p.o. dosing were prepared by adding 95% v/v USP ethanol to either water or reconstituted orange juice for final concentrations of 10 g/100 ml. Doses for the p.o route were, in water, 0.5 g/kg; and, in juice, 0.5, 0.65, 0.95 and 1.25 g/kg administered by constant sipping over 15, 30, 45 and 60 min respectively. A separate dose of 0.5 g/kg in water was used to evaluate the influence of carbohydrate etc. in the orange juice. The increasing times for p.o. dosing were required to accommodate increasing volumes ingested without emesis. All dose preparations were assayed to verify ethanol content.

All eight subjects received each of the three i.v. doses in random sequence with a minimum of 2 weeks between each study. Because of the demanding protocol only the first four of the eight subjects received each of the five p.o. doses in random sequence with 2 weeks spacing. Samples of venous blood were drawn into 10 ml oxalated Vacutainers® beginning with a baseline sample before ethanol administration. Sampling from the arm opposite the ethanol infusion continued 15 min after starting the i.v. dose. Sampling continued 15 min after the p.o dose was finished. Subsequent samples were taken at 15 min intervals during the first hour and at 30 min intervals thereafter until plasma ethanol concentrations had declined below detectable amounts.

Plasma rather than blood ethanol was measured to avoid inter- and intra-subject variation due to differences or changes in haematocrit (Payne, Hill & Wood, 1968). Plasma ethanol concentrations were determined by gas-liquid chromatography (Solon, Watkins & Mikkelson, 1972). The assay was sensitive and reproducible down to plasma ethanol concentrations of 0.01 g/l. Curve-fitting of the plasma ethanol-time data was accomplished using the SAAM-27 computer program (Berman & Weiss, 1977) and a two-compartment open model with Michaelis-Menton elimination from the first compartment and first order gastric absorption (Figure 1). The volume of the first compartment (V_1) was estimated by the computer program and the volume of distribution V_dss) calculated from the relationship: $V_dss = V_1 (1 + K_{12}/K_{21})$. The area under the plasma ethanol-time curve (AUC) was calculated with the trapezoidal method from the beginning of drug administration to the time at which ethanol was not detected.

Classical calculations of ethanol elimination were performed as follows: the slope of ethanol elimination by linear least squares regression of the pseudo-linear portion (excluding upper distribution phase and lower first-order elimination phase); the derived

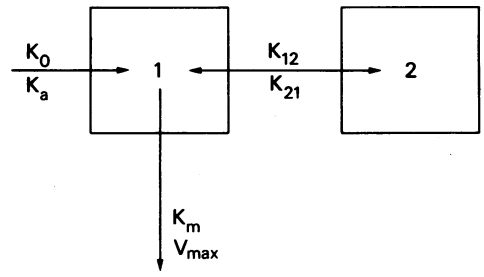

Figure 1 Diagram of model used for computer curve fitting. The central and peripheral compartments are designated by the numbers 1 and 2 respectively. The rate constants for i.v. infusion (zero-order) and p.o. absorption (first order) are K_o and K_a respectively. The transfer rate constants between the central and peripheral compartments are K_{12} and K_{21}. The Michaelis-Menten elimination rate constants are K_m and V_{max}.

ethanol concentration at the start of ethanol administration (Co) from the y-intercept of the regression line; volume of distribution (V_d) by dividing the total dose by Co; and, the total body ethanol elimination rate (Widmark's B_{60}) (Kalant, 1971) from the product of the slope and V_d.

Non-parametric statistical techniques included the Friedman analysis of variance and the Mann-Witney U test (Goldstein, 1964; Hollander & Wolfe, 1973). Non-parametric tests were used because the number of subjects was small and there was no certainty that the data were normally distributed.

Results

Figure 2 is an arithmetic plot of the median concentration-time profiles for each of the p.o. and i.v. doses. Plasma concentrations of ethanol continued to increase after complete ingestion of the two larger p.o. doses. The post-absorption elimination characteristics at all p.o. doses appeared similar as shown by the almost parallel slopes in the pseudo-linear phase; nevertheless, with increasing, p.o. dose there was a trend to progressively steeper decay slopes. A transient decrease in slope appeared following lunch and dinner after the higher doses. On examination of individual data the change in slope with meals was seen in four of four subjects after the dose of 0.95 g/kg; in three of four subjects after the doses of 1.25 and 0.65 g/kg; and in none of the subjects at the lowest dose. After all p.o. doses the plasma decay curves entered a curvilinear phase at concentrations of ethanol below 0.2 g/l.

After i.v. dosing, peak concentrations were greater than after p.o. dosing. After all three i.v. doses, the distribution slopes were much steeper than the ensuing pseudolinear phase. The median distribution

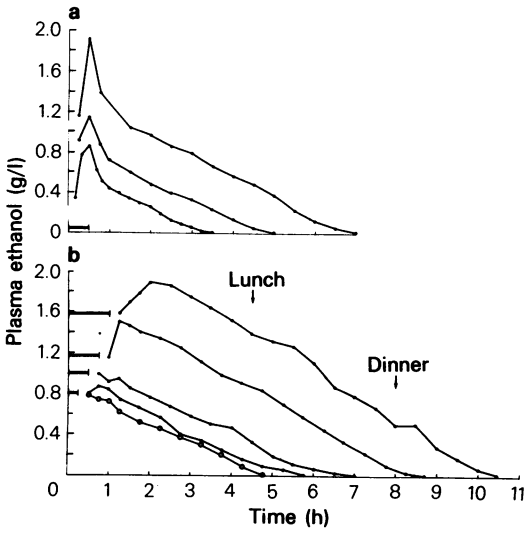

Figure 2 Median plasma ethanol concentrations after each of the i.v. doses ($n = 8$) (a) and p.o. doses ($n = 4$) (b). The open circles indicate p.o. dosing with ethanol in water. The horizontal bars indicate the time of i.v. infusion (similar for all three doses) and time for p.o. ingestion (increasing with dose). See text for details.

half-life calculated by the method of residuals was 9.5 min. The elimination characteristics of all i.v. doses appeared similar as shown by apparent parallel slopes for the pseudolinear phase and resembled those after p.o. doses. However, meals did not change the slopes. A curvilinear disappearance phase similar to that after p.o. dosing was seen at concentrations less than 0.2 g/l.

Table 1 lists the pharmacokinetic measurements related to dose and route of elimination administration. Peak concentrations increased in proportion to dose. This proportionality was confirmed by peak/dose ratios which were constant for each route of administration. Peak/dose ratios were greater after i.v. dosing presumably because the i.v. doses were given over a shorter time. Increasing doses by both routes resulted in disproportionately greater increases in AUC as shown by the progressive increase in the ratio of AUC to dose. The ratios of AUC/dose squared did not vary significantly with either dose or route of administration but a trend of decreasing ratio with increasing p.o. dose was noted.

Table 2 shows the computer-derived pharmacokinetic measurements of ethanol disposition. The median p.o. first-order absorption constant (K_a) of 1.29 h^{-1} indicated almost complete absorption of the bioavailable portion within 1 h. There was a non-linear trend of decreasing K_a with increasing dose in juice but wide variation due to insufficient absorption phase data made differences non-significant. The K_a of ethanol in water was less than the value for the same dose in juice. The volume of distribution at steady state (V_dss) of 0.47 l/kg and maximum velocity of elimination (V_{max}) of 0.12 g h^{-1} kg^{-1} did not vary with dose or route of administration. The Michaelis-Menton constant (K_m) of 0.03 g/l varied widely between subjects, routes and doses and no differences or trends were detected.

Table 3 lists the classical calculations of ethanol disposition. The correlation coefficient for the slope calculations ranged between 0.95 and 0.99. The median slope was 0.20 g l^{-1} h^{-1}. Although the slope tended to increase with increasing p.o. dose, no significant differences in slopes were detected. The apparent volume of distribution (V_d) was a median of 0.55 l/kg. The velocity of elimination (Widmark's B_{60}) was a median of 0.11 g h^{-1} kg^{-1}. Neither of these two measurements varied significantly with dose or route of administration.

Discussion

In this study, we assessed kinetic parameters of ethanol disposition in normal individuals after larger

Table 1 Pharmacokinetic measurements of ethanol disposition

Route	*Dose (g/kg)*	*Peak (g/l)*	*Peak/ dose*	*AUC* (g l^{-1} h)*	*AUC/ dose*	*AUC/ dose²*
i.v. ($n = 8$)	0.375	0.88 (0.69–1.25)	2.34	1.10 (0.62–1.56)	2.93	7.82
	0.50	1.17 (1.03–1.38)	2.34	2.13 (1.79–2.59)	4.26	8.52
	0.75	1.81 (1.17–2.10)	2.40	4.55 (3.72–5.63)	6.07	8.09
p.o. ($n = 4$)	0.50†	0.94 (0.64–1.3)	1.61	1.91 (1.25–2.12)	3.82	7.64
	0.50	0.90 (0.76–1.04)	1.80	2.16 (1.92–2.38)	4.32	8.64
	0.65	1.04 (0.88–1.20)	1.60	3.14 (2.84–3.58)	4.83	7.43
	0.95	1.54 (1.30–1.77)	1.62	6.37 (5.77–7.03)	6.71	7.06
	1.25	2.02 (1.89–2.12)	1.62	10.70 (9.54–11.37)	8.56	6.85

All values are medians with the range of individual values shown in parentheses.
* AUC – area under the concentration-time curve.
† p.o. ethanol in water, all other p.o. doses in orange juice.

Table 2 Computer derived pharmacokinetic measurements of ethanol disposition

Route	*Dose* (*g/kg*)	K_a (h^{-1})	V_dss (*l/kg*)	V_{max} ($g\,h^{-1}\,kg^{-1}$)	K_m (*g/l*)
i.v. ($n = 8$)	0.375		0.57 (0.37–0.73)	0.12 (0.07–0.16)	0.03 (0.003–0.09)
	0.50		0.48 (0.39–0.57)	0.11 (0.10–0.26)	0.03 (0.002–0.28)
	0.75		0.52 (0.45–0.65)	0.12 (0.11–0.13)	0.02 (0.002–0.06)
p.o. ($n = 4$)	0.50†	1.24 (0.97–10.0)	0.47 (0.40–0.52)	0.10 (0.06–0.18)	0.01 (0.001–0.09)
	0.50	2.12 (0.81–7.48)	0.42 (0.16–0.64)	0.12 (0.09–0.36)	0.19 (0.001–1.13)
	0.65	1.64 (0.49–7.33)	0.29 (0.17–0.50)	0.15 (0.06–0.27)	0.19 (0.01–0.60)
	0.95	1.29 (1.16–2.78)	0.47 (0.43–0.48)	0.12 (0.11–0.14)	0.01 (0.01–0.07)
	1.25	0.13 (0.96–2.0)	0.45 (0.37–0.50)	0.14 (0.12–0.15)	0.08 (0.01–0.13)
Grand median		1.29*	0.47	0.12	0.03

All values are medians with the range of individual values shown in parentheses.
* represents 73% absorption in one hour.
† p.o. ethanol in water, all other p.o. doses in orange juice.

Table 3 Classical calculations of ethanol disposition

Route	*Dose* (*g/kg*)	*Slope* ($g\,l^{-1}\,h^{-1}$)	V_d (*l/kg*)	*Widmark's* B_{60} ($g\,h^{-1}\,kg^{-1}$)
i.v. ($n = 8$)	0.375	0.19 (0.17–0.27)	0.58 (0.47–0.85)	0.11 (0.09–0.16)
	0.50	0.19 (0.17–0.24)	0.55 (0.50–0.61)	0.11 (0.09–0.13)
	0.75	0.20 (0.16–0.23)	0.54 (0.49–0.69)	0.11 (0.10–0.13)
p.o. ($n = 4$)	0.50†	0.21 (0.13–0.21)	0.56 (0.49–0.66)	0.11 (0.08–0.13)
	0.50	0.19 (0.16–0.22)	0.50 (0.44–0.55)	0.10 (0.10–0.13)
	0.65	0.18 (0.16–0.23)	0.51 (0.46–0.61)	0.10 (0.10–0.11)
	0.95	0.22 (0.18–0.27)	0.58 (0.48–0.64)	0.12 (0.11–0.12)
	1.25	0.25 (0.23–0.27)	0.55 (0.150–0.62)	0.12 (0.12–0.13)
Grand median		0.20	0.55	0.11

All values are medians with the range of individual values shown in parentheses.
† p.o. ethanol in water, all other p.o. doses in orange juice.

enteral and parenteral doses and compared the results between classical and Michaelis-Menton kinetic analysis. We confirmed some observations of investigators who used smaller doses and different methods of analysis but also have made several new observations and interpretations.

The gastrointestinal absorption rates of ethanol as measured by K_a decreased with increasing dose but interindividual variation obscured significance. We cannot exclude a volume effect on K_a since increase in dose was accomplished by increasing volume of a fixed ethanol concentration. Wilkinson *et al.* (1977a, b) found a K_a of 25 h^{-1} in contrast to our value of 1.29 h^{-1}. This disparity may be explained by our computer fitting which was performed with limited time-concentration data during ethanol ingestion and without consideration for gastric emptying rates and lag times. Both i.v. and p.o. post-absorption peak concentrations increased in proportion to dose thus confirming for concentrations above 2.0 g/l the observations of Wilkinson *et al.* (1977a, b). The rapid post-i.v. infusion distribution half-life of 9 min agreed closely with Vestal's estimate of 45–60 min, i.e. five half-lives, for complete distribution (Vestal *et al.*, 1977). The brief distribution phase observed after our 30 min infusion time would not have been evident if the infusion had been given over two hours (Wilkinson *et al.*, 1976).

A number of points for discussion were drawn from the changes in AUC with dose and route of ethanol administraiton. The amount of carbohydrate in the juice-ethanol mix did not influence bioavailability since AUC was similar for the water-ethanol mix. This result differs from that of Wilkinson who showed that large doses of carbohydrate in ethanol decreased ethanol bioavailability (Wilkinson *et al.*, 1977b). There does not appear to be any clinically significant first-pass hepatic clearance of ethanol since the AUC p.o. and AUC i.v. are almost identical with the 0.5 g/kg doses. The AUC values at the larger p.o. doses may have been increased slightly by post-prandial decreases in slope. Possible explanations for

this transient post-prandial phenomenon include an inhibitory effect of food on hepatic uptake or enzyme metabolism, a transient decrease in the volume of distribution of ethanol or an assay error in post-prandial plasma.

Using the basic formulas of Michaelis-Menten kinetics, Gibaldi & Perrier (1975) showed that at concentrations greater than the K_m, the AUC varied as the square of the dose. Our data verified this constant relationship of AUC to dose squared for all i.v. doses and the lower p.o. doses. However, for the p.o. doses of 0.95 and 1.25 g/kg, the ratios decreased progressively. This may have been the result of longer ingestion times.

The trend toward steeper slopes with increasing dose may well have resulted from including points from the curvilinear phase (near K_m) in the linear regression for slope. However, when we repeated the scope calculation using only the concentrations between the post-distribution peak and the lower limit of linearity (Co/e) suggested by Wagner (1973) the trend of increasing slope with dose was still evident. These steeper slopes are out of keeping with a true zero order process. This suggests an additional route of elimination. One possible route is renal since Ritchie (1975) stated that urine ethanol concentrations may be 1 to 2 times those in the plasma and depending on urine flow up to 10% of the dose can be eliminated by the kidneys. Unfortunately, we did not measure urinary elimination to confirm this possibility. A second hepatic metabolic route such as the microsomal enzyme oxidizing system (MEOS) may explain our observations (Lieber, 1977). However, when we attempted computer curve fitting on the larger dose data using two simultaneous Michaelis-Menton elimination routes the program repeatedly set one of the elimination routes to zero or produced unacceptably high fractional standard deviations for the Michaelis-Menten constants. This result does not exclude the MEOS as a plausible explanation since a higher K_m could have been obscured by continuing absorption and distribution. A final explanation is that complete saturation of total hepatic alcohol dehydrogenase in intact man does not occur until concentrations are far in excess of 2 g/l.

Because of the slightly steeper elimination slopes with the larger doses we studied the relationship between post-distribution peak ethanol concentration and the time to legal sobriety (i.e. when the concentration declined to the legal limit of 0.8 g/l). This relationship is seen in Figure 3. A linear relationship is seen up to a peak concentration of 1.3 g/l but above this the data points lie above the predicted line. Thus the time to legal sobriety became progressively shorter than that predicted by a linear relationship. This phenomenon can be explained mathematically if we assume that peak concentrations and slopes are linearly proportional to dose. Moreover we have

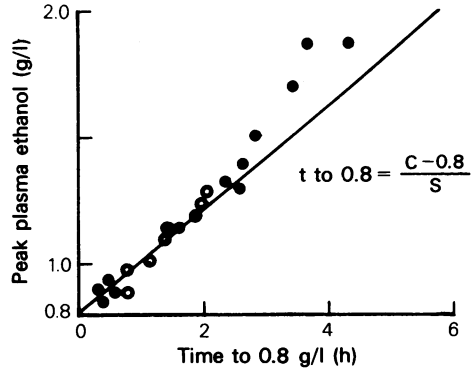

Figure. 3 Relationship of peak post-distribution plasma ethanol concentrations *v* the derived time from peak to 0.8 g/l (from the formula C = peak g/l, S = slope $g\ l^{-1}\ h^{-1}$ as in Table 3). Open circles indicate observations after i.v. doses (n = 8) and closed circles after p.o. doses (n = 13).

made ancillary observations in five patients with ethanol intoxication whose peak concentrations ranged from 3 to 6 g/l. Their data points also fell above the highest points seen in Figure 3 and diverged even more from the line. If we had assumed an average decay slope of 0.30 $g\ l^{-1}\ h^{-1}$ our prediction of their time to sobriety would have been a substantial overestimate. This observation, if confirmed, may have medico-legal implications.

Wagner and Wilkinson suggested that ethanol elimination is dose-dependent based on a direct relationship between initial concentration and slope of the pseudolinear decay (Wagner *et al.*, 1976; Wilkinson *et al.*, 1976). Their slope calculations were performed on portion of lower concentration curve (0.02 to 0.65 g/l). Our calculations of slope were performed on the most linear portions of the pseudo-linear decline where the concentrations ranged from 0.40 to 2.00 g/l. Their dose-dependent change in slope may be an expected artifact of Michaelis-Menten elimination kinetics near and below the K_m. Our dose dependent elimination phenomenon differs in that it occurred at concentrations well above the K_m. It cannot be explained by our kinetic model.

The ethanol volume of distribution by V_dss computation was 0.47 l/kg and was smaller than our V_d value of 0.55 l/kg calculated by the classical method. It is commonly believed that ethanol readily distributes into total body water which represents about 60% of lean body weight or 0.60 l/kg (Ritchie, 1975). The use of this V_d value in calculating a loading dose would result in a higher than expected plasma ethanol concentration. The calculated V_d value is larger because the classical back extrapolation of the elimination curve to the concentration at time = 0 (Co) is assumed to be linear, not pseudolinear, and it thus underestimates Co. In addition, this method

assumes bolus injection with instantaneous distribution into a single compartment. Our value for V_dss was smaller than the V_d of 0.54 to 0.59 l/kg calculated by Wagner and Wilkinson (Wagner *et al.*, 1976; Wilkinson *et al.*, 1976; Wilkinson *et al.*, 1977a, b) using Michaelis-Menten elimination from a one compartment open model, but was similar to that for a subset of subjects in Vestal's studies (Vestal *et al.*, 1977). From the data of his first thirteen patients, whose ages were comparable to the subjects in our study, we calculated a median V_dss of 0.46 l/kg. This close agreement is no doubt explained by our use of a similar kinetic model. We should point out that the intentional overestimate of the volume of distribution used in our dosing compensated for the time of ethanol administration.

The Widmark B_{60} (sometimes erroneously shortened to B) has been the classical parameter used to describe ethanol elimination rated and reported values (Kopun & Propping, 1977) are identical to the rate of 0.11 g h^{-1} kg^{-1} calculated in our study. Comparatively the more rational Michaelis-Menten rate, V_{max} is remarkably similar at 0.12 g h^{-1} kg^{-1}. Vestal's value for V_{max} using an identical computer model was inexplicably 40% less than ours. The 'V_{max}' values reported by Wagner and Wilkinson are given in units customarily used for slope (0.23–0.29 mg ml^{-1} h^{-1}) (Wagner *et al.*, 1976; Wilkinson *et al.*, 1976; Wilkinson *et al.*, 1977). Their maximum elimination rate, the products of their 'V_{max}' and V_d was 0.12 g kg^{-1} h^{-1} and resembled our V_{max} value.

Our median K_m value of 0.03 g/l is within the range of K_m's described by Lieber (1977) for *in vitro* ADH (0.02–0.09 g/l) and is more than tenfold less than his reported K_m for the MEOS. Our median K_m values are slightly less than those obtained by Wagner *et al.* (1976) and Wilkinson *et al.* (1976, 1977a, b.)

In conclusion, ethanol elimination is not a zero-order process. Rather, it is best described by Michaelis-Menten kinetics with unexplained dose-dependent elimination phenomena at higher concentrations.

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